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Discussion

Dr Y. Joseph Woo *(Philadelphia, Pa).* The authors should be congratulated on a great body of work and, as usual, great graphics from Toronto. Are venous endothelial cells the same as arterial endothelial cells, and are they an adequate surrogate if you are using this as a model for allograft vasculopathy and other sorts of arterial problems?

Dr Danny Ramzy *(Toronto, Canada).* Thank you for the question. We have actually performed experiments looking at that question. Between human saphenous vein endothelial cells, human aortic endothelial cells, and human coronary endothelial cells, once you pass the first passage, and all experiments are performed beyond P1, they all behave the same way as ET-1 and other vasoconstrictors and soluble factors. So in terms of using saphenous vein versus aortic cells, the experiments will yield the same results.

Dr Mark J. Krasna *(Baltimore, Md).* Dr Ramzy, could you tell us a little bit about bosentan? It sounds very exciting. Has it been used clinically in your group in any other arena yet?

Dr Ramzy. It has been used clinically. It is approved primarily for primary pulmonary hypertension. It reduces mortality and does reduce pulmonary arterial pressures. It has been used in patients with heart failure, with a few of the studies actually showing harm, likely due to its induction of hypotension. The patient with heart failure died from sudden death, likely from arrhythmia due to

hypotension. So other than in that setting, it has been used safely in patients who can be monitored closely or who have adequate blood pressure. The main problem is the blood pressure.

Dr Krasna. Have either of those groups had any relationship between atherosclerosis and bad outcomes and use of bosentan?

Dr. Ramzy. It has been looked at mostly in allograft vasculopathy in terms of as a surrogate of atherosclerosis, and it does reduce the burden in terms of amount of disease and the degree of stenosis.

Dr John G. Byrne *(Nashville, Tenn).* What do you think are the principal clinical applications of these findings?

D. Ramzy. The clinical applications are severalfold. In terms of atherosclerosis, the reduction of CRP and ET-1 does reduce both the atherosclerotic burden and outcomes such as myocardial infarction. From our results in terms of protein kinase C, we could more specifically target the mechanisms by which CRP results in atherosclerosis and endothelial dysfunction, both in the transplant setting and in atherosclerosis, and especially following transplantation where there is a high degree of vein restenosis, which, if we can modulate basically soluble inflammatory markers like ET-1 and CRP with bosentan or targeted therapy, we could reduce graft restenosis and improve survival and quality of life.

Dr Byrne. Are you talking about a vein graft?

Dr Ramzy. Vein graft.

Dr Turki Albacker *(Montreal, Canada).* Just for my curiosity, for the clinical application of this study, what do you think about the level of CRP in a patient posttransplant and do you think it is high enough to cause atherosclerosis so you can target it with your therapy? Thanks.

Dr Ramzy. There are several studies looking at CRP posttransplant. There are a group of patients who do have elevated levels of CRP, so any level above 3 μg/mL does result in poor outcome. There is actually a recent study that shows any levels above 1.06 ug/mL result in poor outcome. So a slight increase in CRP is able to result in worse outcomes in terms of earlier development of allograft vasculopathy and worse disease, and it has been also shown if you reduce this level, there is a trend toward improvement. Of course, the concentration we used was 25 μg, which is in the intermediate level. We have done studies previous to that. Any level above 3 μg/mL does result in endothelial dysfunction.